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SPECIAL ARTICLE

Do We Need Genomic Research for the Prevention of Common Diseases with Environmental Causes?

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Concerns have been raised about the value of genomic research for prevention and public health, especially for complex diseases with risk factors that are amenable to environmental modification. Given that gene-environment interactions underlie almost all human diseases, the public health significance of genomic research on common diseases with modifiable environmental risks is based not necessarily on finding new genetic ''causes'' but on improving existing approaches to identifying and modifying environmental risk factors to better prevent and treat disease. Such applied genomic research for environmentally caused diseases is important, because 1) it could help stratify disease risks and differentiate interventions for achieving population health benefits; 2) it could help identify new environmental risk factors for disease or help confirm suspected environmental risk factors; and 3) it could aid our understanding of disease occurrence in terms of transmission, natural history, severity, etiologic heterogeneity, and targets for intervention at the population level. While genomics is still in its infancy, opportunities exist for developing, testing, and applying the tools of genomics to clinical and public health research, especially for conditions with known or suspected environmental causes. This research is likely to lead to population-wide health promotion and disease prevention efforts, not only to interventions targeted according to genetic susceptibility.

environment; epidemiology; genomics; health promotion; medicine; preventive health services; preventive medicine; public health

Abbreviations: GSTM1, glutathione *S*-transferase M1; HLA, human leukocyte antigen; MTHFR, methylenetetrahydrofolate reductase.

''*If causes can be removed, then susceptibility ceases to matter.*''

—*Geoffrey Rose*

Since the publication of Geoffrey Rose's article on ''sick individuals and sick populations'' (1), public health practice has downplayed the ''high-risk'' model of prevention in favor

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of a population approach, which may not benefit most persons but can have a large impact on the burden of disease. For example, a small downward shift in the mean serum cholesterol distribution could reduce the burden of coronary heart disease in the population more than treating people with a ''high'' cholesterol level, since most of the burden of heart disease occurs among persons whose cholesterol values are within the ''normal'' range (1, 2).

Now that the Human Genome Project is complete, predictions have become commonplace that drugs, vaccines, and behavioral and medical interventions will soon be tailored according to individual genetic background (3, 4). However, many are skeptical about the added value of genomics in prevention and argue for reinforcing the population approach to prevention, especially for diseases with known environmental causes (5, 6). Merikangas and Risch (7) propose a rationale for prioritizing genomic research on the basis of public health goals. They argue that the highest priority for genomic research should be given to diseases with the strongest evidence of genetic etiology (from heritability analysis), a high public health impact, and limited ability to modify exposures. They base this rationale not only on the difficulties in identifying genes for complex diseases but also on the malleability of environmental risk factors, citing examples such as Alzheimer's disease, autism, and schizophrenia. They state that ''the major preventable environmental causes of illness and death are tobacco use, unhealthy diet, physical inactivity, excess alcohol use, infections, trauma, and exposure to environmental toxins'' (7, p. 600). They suggest that for those modifiable causes of disease, genomic research should have a lower public health priority, because a population approach to prevention will achieve a greater public health benefit than intervention targeted to high-risk groups on the basis of genotypes.

Here we discuss the public health significance of applied genomic research for common diseases with known or suspected environmental risk factors. Because almost all human diseases result from interactions between genetic variants and the environment, suggesting that genomic research will not contribute to preventing conditions with known environmental risk factors could perpetuate the false competition between nature and nurture. For example, Berrettini et al. (8) highlight that although we know that smoking and drugs cause disease, they also cause addiction, undermining interventions focused exclusively on the causative environmental agents. They point out that new knowledge derived from applied genomic research could lead to new pharmacologic and behavioral methods of combating addiction to tobacco and drugs.

Here we make the case that the major objective of applied genomic research for conditions with environmental causes is not necessarily discovering new genetic ''causes'' of disease but supplementing and improving existing approaches to treatment and prevention. In particular, we argue that applied genomic research is as important for conditions with environmental causes as for those without known environmental determinants. We use the term ''genomics'' to refer to emerging technologies for studying genes, gene expression, and gene products and interactions, encompassing other ''-omics'' fields like proteomics and transcriptomics. We define ''applied genomic research'' as clinical and epidemiologic research that characterizes genetic variants in populations, assesses gene-environment interaction, and evaluates genetic tests for screening and prevention (research that answers the question ''What do you do with a gene when you find one?''). We extend this definition to include behavioral and social science research assessing the impact and value of genomic information in clinical practice and disease prevention. None of the ideas in this review are novel, but we hope that this synthesis provides an overall perspective on the potential value of such research without overselling it.

PUBLIC HEALTH SIGNIFICANCE OF APPLIED GENOMIC RESEARCH ON DISEASES WITH ENVIRONMENTAL CAUSES

Applied genomic research has a role to play in three areas: 1) to help stratify disease risks and target interventions to achieve not only individual health promotion goals but overall population health benefits; 2) to identify unknown environmental risk factors for disease or confirm suspected environmental risk factors using such evolving tools as toxicogenomics, gene-environment interaction analysis, and ''Mendelian randomization;'' and 3) to characterize disease occurrence in populations in terms of transmission, natural history, and etiologic heterogeneity and identify biologic targets for intervention such as drugs and vaccines. Although most clinical applications of genomics are not ready for widespread use, there is an increasing need to develop, evaluate, and integrate genomic tools into clinical and public health research.

Stratifying risks and targeting interventions

For many common chronic diseases, such as coronary heart disease, cancer, and diabetes, we already know that modifiable, nongenetic risk factors have high population attributable risks (80–90 percent) (6). These factors include cigarette smoking, a low-quality diet, a sedentary lifestyle, and lack of adherence to recommendations for screening and early disease detection. Because gene-environment interactions underlie almost all human diseases, a high population attributable risk due to environmental factors does not preclude a high population attributable risk due to genes. Interaction among genetic and environmental factors allows the total contribution of individual risk factors to exceed 100 percent, as reflected in Rothman's quote: ''It is easy to show that 100 percent of any disease is environmentally caused and 100 percent is inherited as well'' (9, p. 14).

Nevertheless, it is not obvious why we should study genetic susceptibility to these conditions if we know how to prevent them through manipulation of the environment. One reason may be that our current public health approaches to prevention have not been adequate. For example, more than 60 percent of Americans do not get enough physical activity (10); 21 percent are obese (11). An increasing proportion of US adults have the ''metabolic syndrome'' (a major risk

factor for diabetes and cardiovascular disease) (12), and only 44 percent adhere to recommendations related to colorectal cancer screening (13). Furthermore, identifying an environmental risk factor may not be sufficient to suggest the appropriate intervention. For example, in spite of the reported protective effects of diet and exercise on the risk of developing type 2 diabetes mellitus, we don't know whether ''lifestyle interventions have lifetime effects, or that they prevent diabetes in all subjects, or that these treatments are effective for the most obese patients'' (14). Why not develop and test genomic tools that would help us understand and stratify disease risks so we could create interventions that could generate population health benefits? We will review here two potential tools for ''genomic'' stratification: family history and ''genomic profiling.''

Use of family history for disease prevention and public health. Family medical history is the simplest applied ''genomic tool'' available in practice today. Family history is a risk factor for almost all diseases of public health significance, including most chronic diseases such as coronary heart disease, diabetes, cancer, osteoporosis, and asthma (15). Family history reflects the consequences of shared genetic variations at multiple loci (first-degree relatives such as siblings have 50 percent of their genes in common), shared exposures and responses to environmental factors, and shared behaviors. Only occasionally does a family history of a condition point to a classical genetic disorder (15). More often, the presence of a family history reflects unmeasured genetic and environmental effects and is an indicator of higher risk for the same disease in comparison with the average population risk (16, 17). Yet the collection and interpretation of family history information is often not applied in preventive medicine to assess disease risk, influence early detection, or encourage prevention strategies (18).

Methods have been proposed for quantifying the risk associated with family history based on the number of family members affected, the degree of closeness of the relatives affected, and age at onset of disease (18). On the basis of these parameters, family history can be used for stratification of people into average-risk (general population), moderate-risk, and high-risk groups (19). Scheuner et al. (20) showed that while only a few people fall into the high-risk group (meriting more extensive evaluation and possibly genetic analysis), many more fall into the moderate-risk group for common chronic diseases such as cancer and diabetes. Because a large fraction of the population is likely to have a family history of one or more common diseases, augmenting the population approach to prevention with an approach focused on higher-risk families may help us reach overall public health goals. For example, population-based family studies in Utah have shown that 14 percent of Utah families have a positive family history of coronary heart disease; these families account for 72 percent of all early coronary heart disease events (before age 50 years) and 48 percent of coronary heart disease events at any age. Likewise, the 11 percent of Utah families with a positive family history of stroke account for 86 percent of all early strokes (16). These data suggest that the implementation of family-centered interventions could lead to overall population health benefits. An advantage of a family-centered approach to prevention is that it does not focus exclusively on genetic factors but works within a framework of biologic and cultural relationships to affect risk factor reduction.

Tyagi and Morris (21) showed that because of the low population uptake of colorectal cancer screening, the number of colorectal cancer cases prevented in the population could be doubled by delivering colorectal cancer screening to the 10–15 percent of the population with a family history, even though only a small fraction of these persons have recognized genetic conditions associated with colorectal cancer. The use of family history for colorectal cancer screening should supplement rather than compete with the general recommendations for colorectal cancer screening directed toward the ''average'' group in the population, because most cases occur in people without a family history of colorectal cancer.

The added value of a family history risk-stratification tool should be rigorously tested as an adjunct to population-level prevention activities. Persons at average risk would be encouraged to adhere to standard public health prevention recommendations. Persons with increased risk (i.e., those classified as being at high and moderate risk) would be given personalized recommendations specific to their familial risk that included assessment and modification of risk factors, lifestyle changes, alternative early detection strategies, and chemoprevention. Persons at high risk would also need assessment for possible genetic disorders; this could include counseling, education, and possible genetic testing. Because of the difficulty of implementing general risk stratification in practice, the ultimate success of a prevention strategy that includes family history stratification will depend on the value of family history as a motivator for behavioral change in both health-care providers and people at risk. Screening among people with a family history of colorectal cancer must be increased without causing complacency among persons who are at ''average'' risk because of a negative family history (19). The interest in family history as an additional tool for health promotion has been discussed by the US Surgeon General (22).

Use of genomic tests for targeting environmental interventions. In addition to the current use of family history as a ''genomic tool,'' we could also anticipate the future use of tests for multiple genetic variants (so called ''genomic profiles'') conferring disease susceptibility (23). Many genetic polymorphisms are prevalent in the population; some are associated with increased risks of disease (relative risks of 2–6) of the same order of magnitude as family history (15, 18). The concept of combining multiple genetic variants has been illustrated in hypothetical scenarios of the future practice of medicine (24). Although testing for common genetic polymorphisms is currently not available for clinical practice (25), several companies in the United States and the United Kingdom are prematurely offering genomic profiling for susceptibility to various conditions, including cardiovascular disease, cancer, and infectious diseases (23, 25). Although genomic profiling can be shown theoretically to increase disease predictive value and may eventually be useful for targeting interventions (23), we need much more applied research in this area, including

both epidemiologic studies to provide evidence of gene-disease associations and controlled clinical trials to demonstrate the net utility of such information. In addition, although procedures are not ready now, in the future persons at moderate or high risk on the basis of a family history of disease could be stratified even further, depending on the results of testing for multiple gene variants (26). Ultimately, the promise of applied genomic research for prevention will depend on developing and implementing different types of behavioral and environmental interventions for average-, moderate-, and high-risk groups that lead to overall health benefits for the entire population.

Identifying environmental causes of human disease

Although environmental factors play an important role in the etiology of almost all human diseases, they are often difficult to pinpoint because of changes in exposures over time, correlation of exposures (e.g., dietary variables), and the inability to measure and characterize such exposures. The inability to accurately measure exposures could lead to underestimation of the role of the environment in gene-environment interaction research, as was shown in the recent elegant analysis by Vineis (27). The advent of ''-omics'' technologies (including not only genomics but also transcriptomics and proteomics) is generating an emerging set of tools with which to better quantify environmental exposures (28).

Investigators in applied genomic research are exploring at least three conceptual areas to improve our understanding of the role of environmental factors in disease causation: 1) toxicogenomics, 2) gene-environment interactions, and 3) Mendelian randomization. All three fields are still in their infancy and will require substantial additional methodological development.

Toxicogenomics: using gene and protein expression as markers of exposures. Gene expression technology can enhance our ability to understand the actions of chemicals and environmental agents in biologic systems. The capacity to array large numbers of individual gene fragments on small matrices that can be hybridized to mRNA or cDNA has made it possible to assess the variety of effects of specific chemical exposures. These technologic advances have created the field of toxicogenomics, which uses both RNA and protein expression technologies to study chemical effects on biologic systems (29). Early experiments suggest that gene expression profiles can be used as chemical-specific ''signatures'' (30, 31). Host gene expression signatures may also be useful in identifying pathogen-specific human immune responses (32). Although these technologies have great future potential, their application is still limited in epidemiologic investigations because of challenges in establishing validity and reliability (33).

Gene-environment interaction: the biologic plausibility of exposure-disease associations. As epidemiologists continue to conduct investigations to discover environmental causes of human disease, assessing the biologic plausibility of associations between exposures and outcomes can strengthen causal interpretation of the results. Increasingly, analysis of gene-environment interaction will provide an important approach to strengthening the biologic plausibility of exposure-disease associations (34). For exposures with weak to moderately strong associations with disease outcomes (e.g., odds ratios of 1.5–2.0), causal inference can be strengthened if the data show a stronger effect in a susceptible subgroup of the population. Susceptibility can be due to variations in genes related to metabolic pathways of exposure (e.g., uptake, transport, binding, and clearance). In fact, weak associations may mask important unmeasured biologic susceptibility to the effects of exposure in population subgroups (35). Several examples of gene-environment interaction have been reported recently, such as the relations of folate intake and folate-metabolism genes to cancers and birth defects; the relations of carcinogens and phase I and II enzymes to various cancers; and the relations of oral contraceptives and thrombosis pathway genes to venous thromboembolism (see relevant chapters in *Human Genome Epidemiology* (36)).

Methods of analyzing gene-environment interaction continue to evolve as more genes and more biologic pathways are studied, contributing to the future potential to analyze epidemiologic data on exposure-disease associations that are stratified a priori by genetic susceptibility factors. Demonstrating effect modification in such studies can enhance their overall biologic plausibility.

Mendelian randomization: the use of gene-disease associations to identify exposures. Associations between exposures and diseases in epidemiologic studies are often confounded by unmeasured factors, in spite of efforts to optimize the conduct of these studies. Genomic information could enhance causal inference from associations between environmental factors and human diseases by way of Mendelian randomization (37). As reviewed by Davey Smith and Ebrahim (37), Mendelian randomization—the random assortment of genes from parents to offspring that occurs during meiosis—provides an indirect method of assessing the causal nature of environmental exposures, since certain genotypes can be viewed as proxies for certain exposures. The association between a disease and a polymorphism that mimics the biologic relation between a proposed exposure and disease is viewed as protected from the potential confounding that may occur in observational studies of exposures.

The concept of Mendelian randomization can be illustrated using the example of the single polymorphic variant *C677T* of the methylenetetrahydrofolate reductase (*MTHFR*) gene, which results in reduced enzyme activity (37). The enzyme is involved in the conversion of 5,10-methylenetetrahydrofolate (from dietary folate) to 5-methyltetrahydrofolate, which is needed for the conversion of homocysteine to methionine. This genetic variant mimics low dietary folate intake, leading to higher levels of homocysteine, and can enhance causal inference on the role of folates in neural tube defects. Thus, epidemiologic studies demonstrating the relation between *MTHFR C677T* and neural tube defects would have provided strong evidence of the beneficial effect of folic acid supplementation even before data became available from controlled clinical trials. While Mendelian randomization has the promise of helping epidemiologists derive better causal inferences from environmental risk

factor-disease associations, there are some caveats (38). Association studies remain susceptible to methodological problems and sources of bias, such as small sample sizes, linkage disequilibrium, population stratification, and gene-gene and gene-environment interactions. Currently, the utility of this approach is further limited by our incomplete understanding of gene functions and biologic pathways important in the pathogenesis of common diseases. As we learn more, the concept of Mendelian randomization may become increasingly useful in epidemiologic studies (39).

Understanding patterns of disease occurrence in populations

From the preceding discussion, it is clear that we view applied genomic research as useful not only for identifying susceptibility and developing targeted interventions but also for understanding and quantifying the role of environmental risk factors. Genomics also provides additional tools for probing disease biology (40) and studying patterns of disease occurrence in populations. Genomic information can be useful for refining case definitions, identifying etiologic heterogeneity, and understanding natural history, even for conditions caused by environmental factors such as chemicals and infectious agents. For example, Furberg et al. (41) used data from a population-based case-control study of breast cancer in North Carolina to assess the etiologic heterogeneity of breast cancer according to p53 protein expression status. Prolonged oral contraceptive use was more strongly associated with p53-positive breast cancer (odds ratio = 3.1, 95 percent confidence interval: 1.2, 8.1) than with p53-negative breast cancer (odds ratio = 1.3, 95 percent confidence interval: 0.6, 3.2) among younger women. While this study requires replication, it may suggest that use of oral contraceptives among young women could cause breast cancer through a pathway involving p53 alterations.

Genetic analysis can also be used to increase our understanding of the natural history of environmentally induced diseases, suggesting population-level interventions. For example, Romieu et al. (42) reported that asthmatic children in Mexico with the glutathione *S*-transferase M1 (*GSTM1*) null genotype experienced a significant ozone-related decrement in pulmonary function, while children with the normal *GSTM1* genotype did not. Furthermore, they reported that supplementation with the antioxidant vitamins C and E mitigated ozone-related decline in forced expiratory flow, a protective effect that was stronger in children with the *GSTM1* null genotype. If confirmed in other studies, these results will shed some light on the biologic basis of an environmentally induced condition. Asthmatic children with a genetic deficiency of *GSTM1* may be more susceptible to the deleterious effects of ozone on the small airways and may derive greater benefit from antioxidant supplementation (42). Perhaps most importantly, these findings suggest that a simple intervention—antioxidant vitamin supplementation—could be administered to all children with asthma, producing general benefits for all and specific benefits for those susceptible to ozone. Without such genotype-specific analyses, an important potential intervention could have been overlooked.

A potentially important application of genomics in the study of environmentally caused diseases is its application to public health investigations of acute outbreaks in communities (43). Such studies are conducted by public health agencies to evaluate outbreaks of disease often associated with infectious agents and environmental exposures. These studies typically evaluate demographic, behavioral, and exposure-related risk factors, define the spectrum of disease, and measure the impact of control measures. In infectious disease outbreaks, studies of pathogen genomics are also routinely conducted to help assess source and transmission. The Institute of Medicine's report on microbial threats highlighted the importance of research on interactions between pathogens and human genetic susceptibility (44).

Public health agencies have begun to incorporate human genomics into some investigations, such as an investigation of a leptospirosis outbreak among athletes at a 1998 triathlon competition (45). Leptospirosis often results in subclinical disease, but in 5–10 percent of symptomatic cases it can produce severe outcomes, including cardiovascular and renal complications. In the triathlon study, 98 of 887 triathletes became clinically ill following a swimming competition in a local lake. Swallowing infested lake water was found to be a significant risk factor associated with seropositivity for leptospirosis. Analysis of human leukocyte antigen (HLA) genotypes found that *HLA-DQ6*-positive triathletes had increased risk of laboratory-confirmed leptospirosis in comparison with *DQ6*-negative athletes. *DQ6*-positive triathletes who swallowed lake water had the greatest risk (45). This finding, if confirmed in other studies, can strengthen our understanding of disease occurrence and causality in community outbreaks.

Another example of an emerging public health threat with variable outcomes in terms of infection, transmission, and severity is severe acute respiratory syndrome. Among exposed persons, only some become ill; among persons who develop illness, some are more severely affected; and some patients transmit the virus more effectively than others (super-spreaders). Although few studies have focused on host genomic factors in severe acute respiratory syndrome (46, 47), future investigations will undoubtedly examine such factors further in relation to susceptibility, outcome, transmission, and interaction with environmental factors. Patterns of occurrence of tuberculosis in populations also support important roles for human genomic factors in susceptibility, disease severity, and response to treatment (48–50).

Studying genomic factors in the occurrence of infectious disease in populations can provide insight into prospects for intervention with drugs and vaccines. For example, studies of resistance to human immunodeficiency virus transmission based on host genomic factors (such as C-C chemokine receptor 5 and HLAs) are likely to be valuable in the design of vaccines and drugs to prevent and treat human immunodeficiency virus infection (51).

CONCLUDING REMARKS

In order to achieve individual and population health goals, we need a balanced approach to developing and

applying the tools of genomics (4). Although genomics is still in its infancy, a dichotomous approach that pits nature against nurture in the development of public health priorities in genomics is unlikely to enhance scientific progress or public health practice. Although we know the environmental ''causes'' of many common chronic diseases, we are certainly a long way from achieving health promotion goals for our population. While maintaining healthy skepticism toward the ''hype'' that surrounds evolving technologies, we should strive to develop, validate, and integrate applied genomic tools in our public health research agenda, to assess risks and encourage behavior change in individuals, families, and communities. If such a systematic approach to the evaluation of genetic information is not taken, the potential benefits of the Human Genome Project may never be realized. In addition, because of the difficulties in measuring exposures, genomic tools may help identify additional environmental risk factors and interactions that will improve our understanding of the distribution and determinants of disease in populations. Ultimately, both high-risk approaches to prevention (those targeted toward high-risk subgroups) and population approaches to prevention will be needed. While proven population-based interventions like smoking cessation should be vigorously pursued, they should not compete with the integration of appropriate genetic methods in our public health research armamentarium. As Rose pointed out two decades ago, ''Realistically, many diseases will long continue to call for both approaches, and fortunately competition between them is usually unnecessary'' (1, p. 38). In an editorial on a heritability study of cancer, Hoover wrote, ''Perhaps it is time to drop the competition implied by talking about a debate over nature versus nurture in favor of efforts to exploit every opportunity to identify and manipulate both environmental and genetic risk factors to improve the control of cancer'' (52, p. 136). The same surely applies to other diseases of public health importance.

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